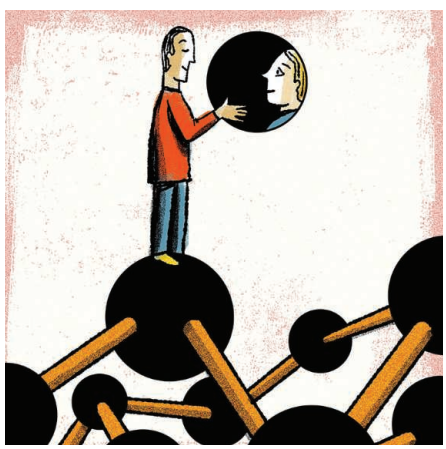
By **Sharon Ann Holgate**

Life inspires applications

At first, the abstract beauty of molecules was what drew David Smith to research. During his school days near Manchester, in the United Kingdom, Smith developed a love for physics. But that was before two chemistry teachers and Linus Pauling's book, *The Nature of the Chemical Bond*, inspired him to read chemistry. For his Ph.D. at the University of Oxford, Smith synthesized molecules that could recognize both positively and negatively charged ions in water and studied how they interact. Applications to chemical sensors were easy enough to envision, but he was focused on the fundamental science. He did a postdoc at ETH Zurich and then, in 1999, won a lectureship at the University of York in the United Kingdom.

In York, inspired by the "beauty and symmetry" of the dendritic organic molecules he had worked on for his postdoc, Smith and his lab members worked to create similar molecules. They soon discovered two molecules that readily self-assembled into gel materials. By 2005, Smith's lab—which by then employed eight people—was building an international reputation for its work on the molecular interactions behind this self-assembling behavior. "We were making small, easily synthesized, programmable molecules"—molecules designed and synthesized with parts that control their behavior—"which assembled on the nanoscale into highly functional materials," Smith says.



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Smith had just begun thinking about how this work might be applied when, in 2005, he met Sam. Sam, who would become Smith's husband, has cystic fibrosis (CF). One potential treatment for CF is gene therapy, and a major challenge in gene therapy is packaging replacement genes so they can be delivered to the target cells. The reversible, noncovalent self-assembly processes Smith's team was studying could be harnessed, he realized, to produce molecular systems that could bind and release DNA. By 2009, half his lab was working on gene therapy. "I didn't know why my work was useful until I was faced with this problem," Smith says.

For a fundamental chemist like Smith, the project represented "a different approach to science," he says. Not only was the work multidisciplinary—spanning chemistry, nanotechnology, biology, and medicine—it also required starting out with specific applications in mind and designing the experiments accordingly.

By 2011, Sam's respiratory function had deteriorated to the point where he needed a lung transplant. Smith took an interest in the drugs used during the surgery. As is common in major operations, heparin, a blood-thinning agent, was injected to prevent clotting; the drug must be removed after surgery to allow the patient's wounds to heal. But some patients are allergic to protamine sulfate, the compound now used to remove heparin from the bloodstream.

Smith realized he could create self-assembled nanoscale systems that, when injected, would hunt down and bind circulating heparin and then be excreted. "We had systems that bound DNA, and they can all, in principle, be used to bind heparin as well …, so we could start pretty much instantly," he says.

Smith encourages young researchers to move into applied research—but only after "you've found fundamental techniques that you're good at," he says. "Be prepared to think and hear about plenty of applications where you cannot really help, in order to find the ones you can approach in an innovative way. Treat the application a bit like an academic problem: Consider which small part of it you may be able to do something about, then work from there."

Sam is unlikely to benefit from Smith's work because he is unlikely to need to. His donor lungs don't have the CF gene mutation, and if things continue to go well, he won't need another major surgery. "The inspiration came from Sam," Smith says, "but I think the benefit is likely to be for others in the future." Knowing that your work could potentially save lives, he says, "helps keep research interesting." ■

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